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A population-based study of the drug interaction between clopidogrel and angiotensin converting enzyme inhibitors

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Clopidogrel can inhibit carboxylesterase 1, which is responsible for the bioactivation of prodrug ACE inhibitors.

WHAT THIS STUDY ADDS

- In subjects receiving clopidogrel following acute myocardial infarction, use of a prodrug ACE inhibitor (ramipril or perindopril) was not associated with an increased risk of adverse cardiovascular events or death relative to lisinopril.
- These findings suggest that the recently described interaction between clopidogrel and prodrug ACE inhibitors is of little clinical relevance.

AIMS

Clopidogrel and angiotensin converting enzyme (ACE) inhibitors are commonly co-prescribed drugs. Clopidogrel inhibits carboxylesterase 1 (CES1), the enzyme responsible for converting prodrug ACE inhibitors (such as ramipril and perindopril) to their active metabolites. The clinical implications of this potential drug interaction are unknown. The clinical consequences of the potential drug interaction between clopidogrel and prodrug ACE inhibitors were examined.

METHODS

We conducted a nested case–control study of Ontarians aged 66 years and older treated with clopidogrel between September 1 2003 and March 31 2013 following acute myocardial infarction. Cases were subjects who died or were hospitalized for reinfarction or heart failure in the subsequent year, and each was matched with up to four controls. The primary outcome was a composite of reinfarction, heart failure or death. The primary analysis examined whether use of the prodrug ACE inhibitors ramipril or perindopril was more common among cases than use of lisinopril, an active ACE inhibitor.

RESULTS

Among 45 918 patients treated with clopidogrel following myocardial infarction, we identified 4203 cases and 14 964 controls. After adjustment, we found no association between the composite outcome and use of perindopril (adjusted odds ratio (aOR) 0.94, 95% confidence interval (CI) 0.76, 1.16) or ramipril (aOR 0.97, 95% CI 0.80, 1.18), relative to lisinopril. Secondary analyses of each element of the composite outcome yielded similar findings.

CONCLUSIONS

Following myocardial infarction, use of clopidogrel with ACE inhibitors activated by CES1 is not associated with an increased risk of adverse cardiovascular outcomes relative to lisinopril. These findings suggest that the recently described drug interaction between clopidogrel and prodrug ACE inhibitors is of little clinical relevance.

Introduction

Angiotensin converting enzyme (ACE) inhibitors are among the most widely prescribed medications in the world, with more than 160 million prescriptions dispensed in the United States in 2011 [1]. They are indicated in the management of various conditions including hypertension, diabetes mellitus, heart failure and left ventricular systolic dysfunction. Their use following acute myocardial infarction reduces the risk of hospitalization for heart failure, reinfarction, and mortality [2–5]. Clopidogrel is a thienopyridine anti-platelet agent dispensed more than 20 million times each year in the United States alone [6]. Like ACE inhibitors, it is widely prescribed to patients following acute myocardial infarction [4, 5]. When added to acetylsalicylic acid in patients with myocardial infarction, clopidogrel decreases the risk of adverse cardiovascular events including reinfarction and mortality [4, 5].

Some data suggest that the available ACE inhibitors are equally effective following acute myocardial infarction [7, 8]. However, important pharmacologic differences exist among the drugs in this class. Most commonly prescribed ACE inhibitors (including ramipril, trandolapril, enalapril and perindopril) are prodrugs that are de-esterified to active metabolites (ramiprilat, trandolaprilat, emalaprilat and perindoprilat, respectively) by the enzyme carboxylesterase 1 (CES1), an enzyme highly expressed in liver and increasingly appreciated as an important factor in drug metabolism [9–12]. In contrast, lisinopril and captopril are active ACE inhibitors that require no such bio-activation [13]. Genetic variation in CES1 has been shown to influence drug metabolism and may influence the antihypertensive effects of ACE inhibitors such as imidapril [11, 14–18].

Importantly, CES1 can be inhibited by other medications and substrates, including clopidogrel [19–22]. Clopidogrel-mediated inhibition of this enzyme has been shown to interfere with the bio-activation of several prodrugs, including oseltamivir and others [19, 20]. Recent findings of Kristensen and colleagues also suggest that ACE inhibitors may competitively inhibit CES1, thereby shunting clopidogrel towards CYP-mediated bioactivation and increasing the concentration of active metabolites *in vitro* [23]. In a population-based sub-study, they found that ACE inhibitors were associated with an increased risk of haemorrhage and adverse cardiovascular events (including cardiovascular death, stroke or reinfarction) in those simultaneously receiving clopidogrel following acute myocardial infarction [23]. However, their primary conclusions compare clopidogrel-treated patients with those not receiving clopidogrel, increasing the possibility of selection bias.

Despite the co-prescription of ACE inhibitors and clopidogrel to millions of patients each year, the clinical relevance of this novel drug interaction is poorly characterized. We examined the clinical consequences of the potential drug interaction between clopidogrel and prodrug ACE inhibitors in a large population.

Methods

Setting and design

We conducted a population-based nested case–control study of Ontario residents aged 66 years or older who commenced treatment with clopidogrel following hospitalization for acute myocardial infarction between September 1 2003 and March 31 2013. These individuals had universal access to hospital care, physicians' services and drug coverage. This study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Canada. The study design is depicted in Figure 1.

Data sources

We used Ontario's administrative health databases which are held securely in linkable files without any direct personal identifiers. We identified prescription drug claims

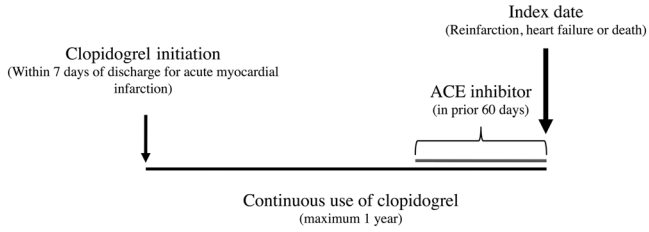

Figure 1

We studied individuals who commenced treatment with clopidogrel within 7 days following hospital discharge for acute myocardial infarction. For each patient, we defined a period of continuous clopidogrel use, beginning with the first clopidogrel prescription and ending with death, hospitalization for heart failure or reinfarction, discontinuation of treatment, 1 year of follow-up or the end of the study period, whichever occurred first

using the Ontario Drug Benefit Database, which includes records of prescriptions dispensed to all Ontarians aged 65 years or older. We obtained hospitalization data from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database, which contains detailed clinical information regarding all hospital admissions, and data on emergency department visits from the CIHI National Ambulatory Care Reporting System. We identified patients with hypertension, diabetes and congestive heart failure using validated disease-specific databases [24–26]. Demographic and mortality data were obtained from the Ontario Health Insurance Plan Registered Persons Database, a registry of all Ontario residents with publically-funded health insurance, and physicians' services were identified using OHIP physician claims data. These databases were linked in an anonymous fashion using encrypted Ontario health card numbers, and are routinely used to study drug safety [27–32].

Study subjects

We identified individuals who commenced treatment with clopidogrel following hospital discharge for acute myocardial infarction, defined as receipt of their first prescription on the day before discharge or within 7 days thereafter. For each patient, we defined a period of up to 1 year of continuous clopidogrel use, beginning with the first clopidogrel prescription and ending with death, hospitalization for heart failure or reinfarction, discontinuation of treatment or the end of the study period, whichever occurred first. Patients were deemed to have discontinued clopidogrel if the interval between successive prescriptions exceeded twice the days supplied by the preceding prescription. In such instances, observation continued until the expiry of the first of these two prescriptions. We did not study patients during their first year of eligibility for prescription drug coverage (age 65 years) to avoid incomplete medication records. To focus on patients newly treated with clopidogrel, we excluded those with any prior use of the drug.

Within the cohort of continuous clopidogrel users, we defined cases as subjects who died or were readmitted to hospital for reinfarction or heart failure within 1 year. We identified hospital admissions using previously validated International Classification of Disease and Related Health Problems (ICD), 10th revision codes for acute myocardial infarction (I21) and heart failure (I50) [25, 33]. We designated the index date as the date of death or hospital admission for reinfarction or heart failure (Figure 1). For patients with multiple such admissions during follow-up, only the first event was considered in the analysis. For each case, we selected up to four controls from the same cohort of clopidogrel-treated patients, matching on the date of index hospitalization, age (within 1 year), gender, calendar year of clopidogrel initiation, and the time between cohort entry and index date (within 30 days). We allowed each control to be matched to only one case. When fewer than four controls were matched to a case, we used only those controls and maintained the matching process. We excluded cases that could not be matched to at least one control, and controls were permitted to become cases at a later date.

We limited the analyses to cases and controls who received a prescription for one of ramipril, perindopril or lisinopril in the 60 days preceding the index date. We selected these agents because they represent the most commonly prescribed ACE inhibitors in Ontario, thereby allowing us to explore the drug interaction of interest while minimizing the number of comparisons. We excluded those who received any other ACE inhibitor, those who received an angiotensin receptor blocker, and those who received more than one ACE inhibitor in the same 60 day period.

Statistical analysis

We used standardized differences to compare baseline characteristics of cases and controls. A standardized difference less than 0.1 indicates good balance between cases and controls for a given covariate [34]. We used conditional logistic regression to estimate the odds ratio and 95% confidence interval (CI) for the association between the composite outcome (death or hospitalization for heart failure or reinfarction) and exposure to either ramipril or perindopril, using lisinopril as the reference group. We adjusted for all variables with a standardized difference exceeding 0.1 between cases and controls. In a secondary analysis, we applied the same analytical approach to each component of the primary outcome separately. To test the sensitivity of our findings, we repeated our analyses using a 100 day look-back period for ACE inhibitor exposure.

All analyses used a two-sided type I error rate of 0.05 as the threshold for statistical significance and were performed at the Institute for Clinical Evaluative Sciences (www.ices.on.ca) using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

Results

During the 10 year study period, we identified 45 918 patients aged 66 years or older who commenced clopidogrel following hospital discharge for acute myocardial infarction. Within this cohort, 9814 subjects died or were hospitalized for reinfarction or heart failure within 1 year while receiving clopidogrel. Of these, 4303 cases received one of lisinopril, ramipril or perindopril in the 60 days preceding their index date. The majority of cases ($n = 4203$, 97.7%) were matched to at least one control ($n = 14\,964$). As expected, case subjects displayed more comorbid illness and greater use of medications for cardiovascular disease and diabetes. The characteristics of case and control subjects are outlined in Table 1.

Table 1

Characteristics of study subjects

Variable	Cases *n* = 4203	Controls *n* = 14 964	Standardized difference
Age (years), median (IQR)	80 (74–85)	79 (73–84)	0.15
66–74	1177 (28.0)	4741 (31.7)	0.08
75–84	1849 (44.0)	7041 (47.1)	0.06
85+	1177 (28.0)	3182 (21.3)	0.16
Female, *n* (%)	1965 (46.8)	6772 (45.3)	0.03
Income quintile, *n* (%)			
1	1019 (24.2)	3192 (21.3)	0.07
2	908 (21.6)	3171 (21.2)	0.01
3	759 (18.1)	2940 (19.6)	0.04
4	775 (18.4)	2857 (19.1)	0.02
5	723 (17.2)	2755 (18.4)	0.03
Missing	19 (0.5)	49 (0.3)	0.02
Residence in long term care facility, *n* (%)	463 (11.0)	606 (4.0)	0.31
Charlson score, *n* (%)			
1	902 (21.5)	7051 (47.1)	
2+	3301 (78.5)	7913 (52.9)	0.53
Coronary interventions, *n* (%)			
Percutaneous coronary intervention	1540 (36.6)	8725 (58.3)	0.44
Coronary artery bypass graft	146 (3.5)	618 (4.1)	0.03
Comorbidities in prior 5 years, *n* (%)			
Hypertension	4028 (95.8)	13 795 (92.2)	0.14
Diabetes	4041 (96.1)	14 031 (93.8)	0.10
Stroke or transient ischaemic attack	334 (7.9)	643 (4.3)	0.17
Myocardial infarction	3965 (94.3)	14 366 (96.0)	0.08
Peripheral vascular disease	325 (7.7)	556 (3.7)	0.19
Chronic liver disease	163 (3.9)	391 (2.6)	0.08
Chronic kidney disease	937 (22.3)	1710 (11.4)	0.32
Congestive heart failure	3,605 (85.8)	13 211 (88.3)	0.08
Atrial fibrillation	964 (22.9)	2003 (13.4)	0.27
Cardiac dysrhythmia	1298 (30.9)	3031 (20.3)	0.26
Angina	2808 (66.8)	11 115 (74.3)	0.17
Cardiomyopathy	79 (1.9)	151 (1.0)	0.08
Number of prescription drugs, median (IQR)*	16 (12–21)	12 (9–17)	0.59
Medication use in preceding 90 days, *n* (%)			
Amiodarone	242 (5.8)	476 (3.2)	0.14
Aspirin and other anti-platelet drugs	431 (10.3)	1560 (10.4)	0.01
β-adrenoceptor blockers	3474 (82.7)	12 093 (80.8)	0.05
Calcium channel blockers	1342 (31.9)	3733 (24.9)	0.16
Digoxin	462 (11.0)	698 (4.7)	0.27
Fibrates	69 (1.6)	200 (1.3)	0.03
Insulin	528 (12.6)	851 (5.7)	0.27
Loop diuretics	2243 (53.4)	3793 (25.3)	0.62
Nitrates	2663 (63.4)	8002 (53.5)	0.20
Non-ASA NSAIDs	422 (10.0)	1489 (10.0)	0.00
Novel oral anticoagulants	7 (0.2)	26 (0.2)	0.00
Non-loop diuretics	606 (14.4)	2298 (15.4)	0.03
Oral glucose-lowering drugs	1054 (25.1)	2505 (16.7)	0.22
Other antihypertensive agents	71 (1.7)	112 (0.7)	0.10
Spironolactone	423 (10.1)	676 (4.5)	0.24
Statins	3648 (86.8)	13 649 (91.2)	0.15
Warfarin	631 (15.0)	1387 (9.3)	0.19

ASA, acetylsalicylic acid; NSAID, non-steroidal anti-inflammatory drug; IQR, interquartile range. *In prior year.

In the primary analysis, we found that compared with clopidogrel recipients receiving lisinopril, no increased risk of death, heart failure or reinfarction was apparent among those receiving perindopril (adjusted odds ratio 0.94, 95% CI 0.76, 1.16; Table 2) or ramipril (adjusted odds ratio 0.97, 95% CI 0.80, 1.18; Table 2). In a secondary analysis examining each component of the primary outcome individually, we found no significant association between death or readmission for either reinfarction or heart failure and use of perindopril or ramipril in the preceding 60 days, relative to lisinopril (Table 3). Analyses in which the look-back period for ACE inhibitor use was extended to 100 days yielded similar findings.

Table 2

Risk of death or hospitalization for heart failure or reinfarction during clopidogrel therapy, by ACE inhibitor

	Cases *n* = 4203	Controls *n* = 14 964	Adjusted odds ratio (95% CI)
Primary analysis*			
Lisinopril	183 (4.4)	504 (3.4)	1.00 (reference)
Perindopril	703 (16.7)	2,763 (18.5)	0.94 (0.76, 1.16)
Ramipril	3317 (78.9)	11 697 (78.2)	0.97 (0.80, 1.18)

*Adjusted for age, income quintile, long term care residence, Charlson comorbidity score, hypertension, diabetes, stroke, peripheral vascular disease, chronic kidney disease, percutaneous coronary intervention, cardiac dysrhythmia, angina, total number of distinct drugs, amiodarone, calcium channel blockers, digoxin, insulin, loop diuretics, nitrates, oral glucose-lowering drugs, other antihypertensive agents, spironolactone, statins and warfarin.

Discussion

In this population-based study spanning over a decade, we found that among older individuals newly commencing clopidogrel following acute myocardial infarction, use of ramipril or perindopril (prodrug ACE inhibitors activated by CES1) was not associated with an increased risk of reinfarction, heart failure or death relative to lisinopril (an active ACE inhibitor). These findings suggest that the recently described drug interaction between clopidogrel and prodrug ACE inhibitors is of little clinical relevance.

CES1 is involved in the bio-activation of prodrug ACE inhibitors and is competitively inhibited by clopidogrel *in vitro* [19, 20]. A recent study by Kristensen and colleagues examined the potential clopidogrel–ACE inhibitor drug interaction and observed a modest increase in the risk of adverse cardiac events (acute myocardial infarction, cardiovascular death or stroke) in patients prescribed clopidogrel with an ACE inhibitor relative to those prescribed an ACE inhibitor alone (hazard ratio 1.12, 95% CI 1.06, 1.19) [23]. This finding may reflect baseline differences in the characteristics of patients treated with clopidogrel relative to those who are not. By restricting our analysis to older individuals with ongoing use of clopidogrel and an ACE inhibitor, we examined a relatively homogenous population, and minimized selection bias by limiting the analysis to patients receiving one of three commonly prescribed ACE inhibitors. We assert that if clopidogrel inhibits CES1 in a clinically meaningful

Table 3

Risk of each outcome among clopidogrel recipients, by ACE inhibitor

	Cases	Controls	Adjusted odds ratio (95% CI)
Secondary analysis			
Reinfarction*	*n* = 1832	*n* = 6976	
Lisinopril	82 (4.5)	234 (3.4)	1.00 (reference)
Perindopril	314 (17.1)	1 299 (18.6)	1.10 (0.81, 1.50)
Ramipril	1436 (78.4)	5 443 (78.0)	1.10 (0.83, 1.47)
Heart failure†	*n* = 2069	*n* = 7771	
Lisinopril	90 (4.3)	294 (3.8)	1.00 (reference)
Perindopril	328 (15.9)	1353 (17.4)	1.02 (0.75, 1.40)
Ramipril	1651 (79.8)	6124 (78.8)	1.10 (0.83, 1.45)
All-cause mortality‡	*n* = 1953	*n* = 7234	
Lisinopril	78 (4.0)	228 (3.2)	1.00 (reference)
Perindopril	306 (15.7)	1394 (19.3)	0.83 (0.59, 1.18)
Ramipril	1569 (80.3)	5612 (77.6)	0.97 (0.70, 1.34)

*Adjusted for age, income quintile, long term care residence, Charlson comorbidity score, stroke, peripheral vascular disease, chronic kidney disease, congestive heart failure, percutaneous coronary intervention, coronary artery bypass graft, cardiac dysrhythmia, angina, total # of drugs, calcium channel blockers, digoxin, insulin, loop diuretics, nitrates, oral glucose-lowering drugs, spironolactone, statins, warfarin. †Adjusted for age, income quintile, long term care, Charlson comorbidity score, hypertension, peripheral vascular disease, chronic liver disease, congestive heart failure, coronary artery bypass graft, cardiomyopathy, myocardial infarction, total number of drugs, amiodarone, calcium channel blockers, digoxin, insulin, loop diuretics, nitrates, oral glucose-lowering drugs, other antihypertensive agents, spironolactone, warfarin. ‡Adjusted for age, income quintile, long term care residence, Charlson comorbidity score, hypertension, diabetes, stroke, peripheral vascular disease, chronic liver disease, chronic kidney disease, congestive heart failure, percutaneous coronary intervention, cardiac dysrhythmia, angina, myocardial infarction, total number of distinct drugs, amiodarone, digoxin, insulin, loop diuretics, nitrates, Oral glucose-lowering drugs, other antihypertensive agents, spironolactone, statins, warfarin.

way, this would impair bioactivation of prodrug ACE inhibitors, attenuating their clinical benefit. If this were the case, patients taking clopidogrel with either rampiril or perindopril (prodrug ACE inhibitors activated by CES1) should be more prone to adverse cardiovascular events than patients taking clopidogrel with lisinopril (an active ACE inhibitor). We found no such differences, suggesting that this recently described interaction is unlikely to be of clinical relevance.

Although clopidogrel can clearly inhibit CES1 *in vitro*, there are several reasons why this observation may not be clinically relevant. First, clopidogrel concentrations used in drug inhibition studies (20–50 μM) are generally much higher than those achieved *in vivo* after a 75 mg oral dose (2.2–2.5 ng ml^{-1}) [19, 20]. Second, clopidogrel is highly protein bound (>98%) and unbound clopidogrel will constitute only a small fraction of total drug concentrations. This is important because unbound drug concentrations are a more important determinant of enzyme inhibition than total drug concentration in plasma [35]. Third, clopidogrel concentrations decline quickly from maximal concentrations (t_{max} = 60 min, $t_{1/2}$ = 6 h), and any inhibition of ACE inhibitor metabolism may therefore be temporary.

Some limitations of our study warrant emphasis. Our conclusions derive from patients aged 66 years and older, and the generalizability of our findings to younger patients is unknown. Although we used validated outcome definitions with high sensitivity and specificity [25, 33], some degree of outcome misclassification is likely. Importantly however, this applies equally to all the ACE inhibitors we studied. We did not examine all available ACE inhibitors, choosing instead to focus on the agents most widely prescribed in Ontario, with the rationale that this would be sufficient to confirm or refute a clinically important drug interaction while minimizing unnecessary comparisons. Although we adjusted for several clinical covariates, we did not have information on non-prescription drug use and other important factors including smoking and other lifestyle factors, and the adequacy of control of hypertension, blood glucose or dyslipidaemia. Again, these limitations apply equally to ramipril, perindopril and lisinopril, although we may not have been able to adjust for any residual differences in these characteristics between exposure groups. Finally, there was some degree of imbalance between cases and controls due to the nature of design. This is expected, because cases are defined by the occurrence of an adverse outcome but controls are not. Regardless, the key comparison in our study is not between cases and controls, but rather between ACE inhibitor type (prodrug *vs*. active drug).

In conclusion, among older individuals commencing clopidogrel therapy following acute myocardial infarction, use of the prodrug ACE inhibitors ramipril or perindopril was not associated with an elevated risk of recurrent myocardial infarction, heart failure or death relative to use of lisinopril. These results offer a measure of reassurance that the recently described interaction between clopidogrel and prodrug ACE inhibitors is of little relevance to patients taking these medications concomitantly.

Competing Interests and Financial Disclosure

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work. During the past 3 years, Muhammad M. Mamdani has been on advisory boards and/or received honoraria from Astra Zeneca, Bristol-Myers Squibb, Eli Lilly and Company, Glaxo Smith Kline, Hoffman La Roche, Novartis, Novo Nordisk and Pfizer. None of the other authors have any conflicts of interest to disclose and there are no other relationships or activities that could appear to have influenced the submitted work.

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Author Contributions

Study concept and design: AMC, EMM, KAF, TG, JMP, MMM, DNJ
Analysis and interpretation of data: AMC, EMM, KAF, TG, DNJ
Acquisition of data: KAF
Drafting of the manuscript: AMC, EMM, DNJ
Critical revision of manuscript: AMC, EMM, TG, KAF, JMP, MMM, DNJ

All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1 IMS Institute for Health Informatics. The Use of Medicines in the United States: Review of 2011. Available at https://www.imshealth.com/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/IHII_Medicines_in_U.S_Report_2011.pdf (last accessed 30 May 2014).

2 Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, Torp-Pedersen C, Ball S, Pogue J, Moye L, Braunwald E. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet 2000; 355: 1575–81.

3 Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. Circulation 1998; 97: 2202–12.

4 Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ. AHA/ACC Guideline for the management of patients with non-ST-elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 130: e344–426.

5 O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW. American College of Cardiology Foundation/American Heart Association Task Force on Practice G. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013; 127: e362–425.

6 Snyder D. Pediatric Focused Safety Review: Plavix® (clopidogrel) Pediatric Advisory Committee Meeting 2013. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM369698.pdf (last accessed 30 May 2014).

7 Hansen ML, Gislason GH, Kober L, Schramm TK, Folke F, Buch P, Abildstrom SZ, Madsen M, Rasmussen S, Torp-Pedersen C. Different angiotensin-converting enzyme inhibitors have similar clinical efficacy after myocardial infarction. Br J Clin Pharmacol 2008; 65: 217–23.

8 Tu K, Gunraj N, Mamdani M. Is ramipril really better than other angiotensin-converting enzyme inhibitors after acute myocardial infarction? Am J Cardiol 2006; 98: 6–9.

9 Laizure SC, Herring V, Hu Z, Witbrodt K, Parker RB. The role of human carboxylesterases in drug metabolism: have we overlooked their importance? Pharmacotherapy 2013; 33: 210–22.

10 Zhu HJ, Wang X, Gawronski BE, Brinda BJ, Angiolillo DJ, Markowitz JS. Carboxylesterase 1 as a determinant of clopidogrel metabolism and activation. J Pharmacol Exp Ther 2013; 344: 665–72.

11 Pare G, Eriksson N, Lehr T, Connolly S, Eikelboom J, Ezekowitz MD, Axelsson T, Haertter S, Oldgren J, Reilly P, Siegbahn A, Syvanen AC, Wadelius C, Wadelius M, Zimdahl-Gelling H, Yusuf S, Wallentin L. Genetic determinants of dabigatran plasma levels and their relation to bleeding. Circulation 2013; 127: 1404–12.

12 Hagihara K, Kazui M, Kurihara A, Yoshiike M, Honda K, Okazaki O, Farid NA, Ikeda T. A possible mechanism for the differences in efficiency and variability of active metabolite formation from thienopyridine antiplatelet agents, prasugrel and clopidogrel. Drug metabolism and disposition: the biological fate of chemicals 2009; 37: 2145–52.

13 Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. Circulation 1998; 97: 1411–20.

14 Geshi E, Kimura T, Yoshimura M, Suzuki H, Koba S, Sakai T, Saito T, Koga A, Muramatsu M, Katagiri T. A single nucleotide polymorphism in the carboxylesterase gene is associated with the responsiveness to imidapril medication and the promoter activity. Hypertension research: official journal of the Japanese Society of Hypertension 2005; 28: 719–25.

15 Zhu HJ, Appel DI, Johnson JA, Chavin KD, Markowitz JS. Role of carboxylesterase 1 and impact of natural genetic variants on the hydrolysis of trandolapril. Biochem Pharmacol 2009; 77: 1266–72.

16 Merali Z, Ross S, Pare G. The pharmacogenetics of carboxylesterases: CES1 and CES2 genetic variants and their clinical effect. Drug Metabol Drug Interact 2014; 29: 143–51.

17 Lewis JP, Horenstein RB, Ryan K, O'Connell JR, Gibson Q, Mitchell BD, Tanner K, Chai S, Bliden KP, Tantry US, Peer CJ, Figg WD, Spencer SD, Pacanowski MA, Gurbel PA, Shuldiner AR. The functional G143E variant of carboxylesterase 1 is associated with increased clopidogrel active metabolite levels and greater clopidogrel response. Pharmacogenet Genomics 2013; 23: 1–8.

18 Zhu HJ, Patrick KS, Yuan HJ, Wang JS, Donovan JL, DeVane CL, Malcolm R, Johnson JA, Youngblood GL, Sweet DH, Langaee TY, Markowitz JS. Two CES1 gene mutations lead to dysfunctional carboxylesterase 1 activity in man: clinical significance and molecular basis. Am J Hum Genet 2008; 82: 1241–8.

19 Shi D, Yang J, Yang D, LeCluyse EL, Black C, You L, Akhlaghi F, Yan B. Anti-influenza prodrug oseltamivir is activated by carboxylesterase human carboxylesterase 1, and the activation is inhibited by antiplatelet agent clopidogrel. J Pharmacol Exp Ther 2006; 319: 1477–84.

20 Thomsen R, Rasmussen HB, Linnet K, Consortium I. *In vitro* drug metabolism by human carboxylesterase 1: focus on angiotensin-converting enzyme inhibitors. Drug metabolism and disposition: the biological fate of chemicals 2014; 42: 126–33.

21 Takahashi S, Katoh M, Saitoh T, Nakajima M, Yokoi T. Different inhibitory effects in rat and human carboxylesterases. Drug metabolism and disposition: the biological fate of chemicals 2009; 37: 956–61.

22 Zhu HJ, Appel DI, Peterson YK, Wang Z, Markowitz JS. Identification of selected therapeutic agents as inhibitors of carboxylesterase 1: potential sources of metabolic drug interactions. Toxicology 2010; 270: 59–65.

23 Kristensen KE, Zhu HJ, Wang X, Gislason GH, Torp-Pedersen C, Rasmussen HB, Markowitz JS, Hansen PR. Clopidogrel bioactivation and risk of bleeding in patients co-treated with ACE inhibitors after myocardial infarction: A proof of concept study. Clin Pharmacol Ther 2014; 96: 713–22.

24 Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. Diabetes Care 2002; 25: 512–6.

25 Schultz SE, Rothwell DM, Chen Z, Tu K. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. Chronic diseases and injuries in Canada 2013; 33: 160–6.

26 Tu K, Campbell NR, Chen ZL, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. Open medicine 2007; 1: e18–26.

27 Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study N Engl J Med 2004; 351: 543–51.

28 Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA 2003; 289: 1652–8.

29 Mamdani M, Juurlink DN, Lee DS, Rochon PA, Kopp A, Naglie G, Austin PC, Laupacis A, Stukel TA. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. Lancet 2004; 363: 1751–6.

30 Juurlink DN, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, Henry DA, Kopp A, Mamdani MM. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009; 180: 713–8.

31 Park-Wyllie LY, Juurlink DN, Kopp A, Shah BR, Stukel TA, Stumpo C, Dresser L, Low DE, Mamdani MM. Outpatient gatifloxacin therapy and dysglycemia in older adults. N Engl J Med 2006; 354: 1352–61.

32 Lipscombe LL, Gomes T, Levesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. JAMA 2007; 298: 2634–43.

33 Juurlink D, Preyra C, Croxford R, Chong A, Austin P, Tu J, Laupacis A. Canadian Institute for Health Information Discharge Abstract Database: a Validation Study. Toronto: Institute for Clinical Evaluative Sciences; 2006.

34 Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. Stat Med 2007; 26: 734–53.

35 Ito K, Iwatsubo T, Kanamitsu S, Ueda K, Suzuki H, Sugiyama Y. Prediction of pharmacokinetic alterations caused by drug-drug interactions: metabolic interaction in the liver. Pharmacol Rev 1998; 50: 387–412.